

124 dihydroxyphenyldecylic acid; 2,5-dihydroxyphenylundecylic acid; methyl ester of 2,5-dihydroxyphenylundecylic acid; 2,5-dihydroxy-3,4-dimethylphenylacetic acid; ethyl-2,5-dihydroxy-4,6-dimethylphenylacetate; 2-(2,5-dihydroxy-4-methylphenyl)-N-octylacetamide; 6-(2,5-dihydroxy-4-methoxyphenyl)hexanoic acid; 4-[(6-methoxytetrahydro-2H-pyran-2-yl)oxy]phenol; 4-[(tetrahydro-2H-pyran-2-yl)oxy]phenol; and 4-[(tetrahydro-2H-thiopyran-2-yl)oxy]phenol.--

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### REMARKS

Claims 1-23 are pending in the application. Reconsideration is respectfully requested.

The present invention relates to cosmetic and dermatological compositions and to the use of such for the depigmentation and/or lightening of the skin, body hair and/or hair of the head.

Applicants' representative wishes to thank Examiners Willis and Hartley for the helpful and courteous interview of February 20, 2002. As a result of the discussion, it is believed that the issues in the case have been clarified and that the prosecution of the application has been materially advanced.

### Objection To Specification

The stated ground of rejection is believed obviated by the amendment made to the specification at page 6, lines 2 and 3 by which incorporation by reference is deleted and in the last two lines on page 18 of the text.

As to the matter of other amendments made to the text of the application, spelling corrections have been made at page 5, line 20 and page 7, last line.

Further identification as to the WO International PCT Application at page 3, lines 21 and 22 has been made.

Claim Rejection, 35 U.S.C. 112, Second Paragraph

The term "derivative thereof" has been objected to as indefinite. This ground of rejection is believed obviated by the deletion of the term in favor of the more definitive term of a hydroquinone compound which has depigmenting or lightening properties. Thus, in order for a derivative of hydroquinone to be within the scope of the present invention, it must have the ability to depigment or lighten the hair or skin. Support for this property can be found amply on page 4 of the text. Entry of the amendment into the record is respectfully requested as it affects Claims 4-7, 9, 10, 12, 15-18, 20 and 21. Withdrawal of the rejection based on 35 USC 112 is requested.

As claimed, the present invention is directed to a composition which is especially effective in depigmenting or lightening the skin or hair and is a combination of N-cholesteryloxycarbonyl-4-para-aminophenol and hydroquinone or a hydroquinone derivative (compound) which is known to have depigmenting and lightening activity when applied to the skin or hair. The discussion on pages 2 and 3 of the specification clearly indicate that hydroquinone and derivatives thereof are effective as skin depigmenting or lightening agents. However, this class of compounds is known to be cytotoxic and irritating to the skin and therefore concentration limitations are placed on their use in cosmetic formulations. Some aminophenol compounds are also known to be useful as having skin depigmenting activity by inhibiting melanogenesis activity even at low concentrations, without demonstrating cytotoxicity. However, the finding of the present invention is that the specific combination of

N-cholesteryloxy carbonyl-4-para-aminophenol and hydroquinone or a hydroquinone compound is markedly superior as a active agent combination which has the ability to depigment or lighten the skin or hair.

That, in fact, the combination of skin and hair depigmenting or lightening agents of the present invention have especially significant activity is evident from the evidence provided in Examples 1 and 2 of the present application. Example 1 describes a cosmetic formulation formed from N-cholesteryloxycarbonyl-4-p-aminophenol and hydroquinone. The theoretical percentage of inhibition for the mixture at the indicated concentrations is 24.4 %. On the other hand, upon actual testing of a composition containing the two compounds in admixture at the same concentrations gave an observed inhibition of 31.8 %.

The results of Example 1 stand in contrast to the results of Example 2 which provides the inhibitory effect achieved by another aminophenol compound, i. e., N-ethoxycarbonyl-4-p-aminophenol, in combination again with hydroquinone. This time, upon actual testing of the admixture of the two compounds, **no synergistic effect** was exhibited by the combination, since the observed inhibition was 29.4 % which is substantially less than the expected inhibition of the two compounds based on the sum (49.2 %) of the inhibitory effect known for each compound used alone. Accordingly, the enhanced skin/hair lightening or depigmenting effect of the invention is achieved selectively with N-cholesteryloxycarbonyl-4-p-aminophenol and hydroquinone or a hydroquinone compound in combination.

Claims 1-3, 8, 12-14 and 19 stand rejected based on 35 USC 102(b) as anticipated by Philippe et al, WO 99/10318. This ground of rejection is respectfully traversed.

As discussed at the interview, the disclosure of Philippe et al, WO 99/10318 is directed to a skin/hair depigmenting composition based upon an aminophenol compound. N-

ethoxycarbonyl-4-p-aminophenol and N-cholesteryloxycarbonyl-4-p-aminophenol are disclosed as Examples 1 and 3 respectively of the patent, and the skin depigmenting effectiveness of the two compounds is shown in the Table on page 9 of the document is contrasted with kojic acid. At the closest the disclosure of the patent approaches the present invention, mention is made on page 7, lines 15-17 of the patent that a **possibility or option** is to combine any one of the aminophenol compounds disclosed in the patent with kojic acid or hydroquinone or a derivative thereof. The French words "on peut" impart the meaning to the sentence that an option or possible alternative exists to combine an aminophenol compound with hydroquinone or derivative thereof. The sentence in question does not **require** in any way that an aminophenol compound be combined with hydroquinone or derivative thereof. Moreover, **no** example whatever is presented in the text of the patent of an aminophenol compound combined with hydroquinone or derivative thereof, and certainly no example of a combination of N-cholesteryloxycarbonyl-4-p-aminophneol and hydroquinone in a cosmetic composition. (Applicants point out that WO 99/10318 is the patent disclosure discussed at page 3, lines 18-22 of the text and, of course, at page 5, lines 20-22 of the specification. The U. S. equivalent to this patent is application Serial No. 09/284,490 filed June 21, 1999.) Accordingly, it is clear from the discussion above that the combination of an aminophenol compound with hydroquinone or a derivative thereof is not specifically disclosed in the patent, nor is such a combination required, and therefore the patent is not deemed to anticipate the invention as claimed. Presuming that a question of obviousness of the present claims might be raised over the disclosure of the patent, the same is deemed to be obviated by the data in the Examples of the present application as discussed above, which shows superior skin/hair lightening or depigmenting properties for the N-cholesteryloxycarbonyl-4-p-

aminophenol containing composition of Example 1 over the N-ethoxycarbonyl-4-p-aminophenol containing composition of Example 2. Withdrawal of the rejection is respectfully requested.

Claims 1-3, 8, 12-14 and 19 stand rejected based on 35 USC 103(a) as obvious over Philippe et al, WO 99/10318. This ground of rejection is respectfully traversed.

Applicants traverse the obviousness ground of rejection on the basis of the comparative demonstration provided on the record in the Examples of the present specification. There is no teaching or suggestion anywhere in the reference which would lead the skilled artisan to select only N-cholesteryloxycarbonyl-4-p-aminophenol as an aminophenol and use it in combination specifically with hydroquinone or derivative thereof with the expectation of achieving an especially effective depigmenting or lightening effect. Accordingly, the obviousness ground of rejection is believed obviated and withdrawal of the same is respectfully requested.

Support for newly added claim 23 can be found on pages 6-8 of the text. Entry of the claim is respectfully requested.

It is now believed that the application is in proper condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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**MARKED-UP COPY OF AMENDMENT**

**IN THE SPECIFICATION**

Page 2, delete line 2.

Page 3, between lines 24 and 25, insert -- SUMMARY OF THE INVENTION --

Page 3, delete the paragraph of lines 18-22 in favor of the following new paragraph:

-- Various depigmenting agents have thus been proposed. In particular, it has been demonstrated that certain aminophenol derivatives have the property of inhibiting melanogenesis even in low concentrations, without demonstrating cytotoxicity. These compounds, which are described in International PCT Patent Application No. WO 99/10318, (U.S. Patent Application Serial No. 09/284,490 filed June 21, 1999), comprise in particular N-cholesteryloxycarbonyl-4-para-aminophenol. --

Please delete the two paragraphs from page 5, line 20 to page 6, line 10 in favor of the following new paragraphs:

-- [N-cholesterylaxycarbonyl-4-para-aminophenol] N-cholesteryloxycarbonyl-4-para-aminophenol may be obtained as described in U. S. Patent Application Serial No. 09/284,490, filed June 21, 1999, which is incorporated herein by reference. --

-- In the context of the present invention, the term "hydroquinone derivative" is understood to mean optionally substituted hydroquinone monoalkyl ethers and hydroquinone monoaryl ethers. Such hydroquinone ethers are described in Japanese Patent Application Nos. JP-06 192 062 and JP-61 159 943[, which are incorporated herein by reference]. It is also

understood to mean the ethers of hydroquinone and of a heterocyclic alcohol, as described in International PCT Patent Application No. WO 98/07406 (corresponds to U. S. Patent No. 6,139,854), which is also incorporated herein by reference. The expression "hydroquinone derivative" is further understood to include the (2,5-dihydroxyphenyl) carboxylic acid derivatives described, for example, in application EP-526 302 (corresponds to U. S. Patent No. 5,449,518), which is also incorporated herein by reference. This term is additionally understood to include hydroquinone which is substituted, in particular, with alkylthio or alkoxy groups. --

Please delete the paragraph from page 6, line 11 to page 8, line 5 in favor of the following new paragraph:

-- Examples of preferred hydroquinone derivatives include:

2,5-dihydroxyphenyl propionic acid, the ethyl ester of 2,5-dihydroxyphenyl propionic acid; the lauryl ester of 2,5-dihydroxyphenylpropionic acid; methyl 2,5-dihydroxy-3,4-dimethylphenyl acetate; 2,5-dihydroxy-4-methylphenyl acetic acid; alkyl esters of 2,5-dihydroxy-4-methylphenyl acetic acid; 2,5-dihydroxy-4-methylphenyl propionic acid; ethyl ester of 2,5-dihydroxy-4-phenylpropionic acid; 2,5-dihydroxy-4-methylbenzoic acid; methyl ester of 2,5-dihydroxy-4-methylbenzoic acid; ethyl ester of 2,5-dihydroxy-4-methylbenzoic acid; 2,5-dihydroxy-4-ethylbenzoic acid; 2,5-dihydroxy-4-methoxybenzoic acid; methyl ester of 2,5-dihydroxy-4-methoxybenzoic acid; 2,5-dihydroxy-4-ethoxybenzoic acid; 3-(2,5-dihydroxy-4'-methylphenyl)-1-N-( $\omega$ -carboxydecyl)propylamide; 2,5-dihydroxy-4-methylphenylbutanoic acid; 2,5-dihydroxy-4-methylphenylhexanoic acid; 2,5-dihydroxy-4-methoxyphenylacetic acid; methyl ester of 2,5-dihydroxy-4-methoxyphenylacetic acid; 2,5-dihydroxy-4-methoxybenzylamide; methyl 2,5-dihydroxy-3-methoxyphenylacetate; 2,5-dihydroxy-3-methoxyphenylpentadecylic acid; methyl ester of 2,5-dihydroxy-3-methoxyphenylpentadecylic acid; 2,5-dihydroxyphenylbutanoic acid;



methyl ester of 2,5-dihydroxyphenylbutanoic acid; 2,5-dihydroxyphenylbutylamide; 2,5-dihydroxyphenylpentanoic acid; 2,5-dihydroxyphenylhexanoic acid; 2,5-dihydroxyphenyloctanoic acid; 2,5-dihydroxyphenyldecylic acid; methyl ester of 2,5-dihydroxyphenyldecylic acid; 2,5-dihydroxyphenylundecylic acid; methyl ester of 2,5-dihydroxyphenylundecylic acid; 2,5-dihydroxy-3,4-dimethylphenylacetic acid; [ethyl-2,5-dihydroxy-4,6-dimethylphenylacetate] ethyl-2,5-dihydroxy-4,6-dimethylphenylacetate; 2-(2,5-dihydroxy-4-methylphenyl)-N-octylacetamide; 6-(2,5-dihydroxy-4-methoxyphenyl)hexanoic acid; 4-[(6-methoxytetrahydro-2H-pyran-2-yl)oxy]phenol; 4-[(tetrahydro-2H-pyran-2-yl)oxy]phenol; and 4-[(tetrahydro-2H-thiopyran-2-yl)oxy]phenol.--

Page 18, delete the last two lines.

#### IN THE CLAIMS

Please amend Claims 1, 4-7, 9, 10, 12, 15-18, 20, 21 and 23 as follows:

--1. (Amended) A composition, comprising, in a physiologically acceptable medium:

(1) N-cholesteryloxycarbonyl-4-para-aminophenol; and

(2) hydroquinone or a [derivative thereof] hydroquinone compound which has depigmenting or lightening activity.

4. (Amended) The composition of Claim 1, wherein said hydroquinone or [derivative thereof] hydroquinone compound is present in an amount of 0.1 to 2 % by weight, relative to the total weight of said composition.

5. (Amended) The composition of Claim 1, wherein said hydroquinone or [derivative thereof] hydroquinone compound is present in an amount of 0.5 to 1 % by weight, relative to the total weight of said composition.

6. (Amended) The composition of Claim 1, wherein said N-cholesteryloxy carbonyl-4-para-aminophenol is present in an amount of 0.01 to 5 % by weight, relative to the total weight of said composition, and said hydroquinone or [derivative thereof] hydroquinone compound is present in an amount of 0.1 to 2 % by weight, relative to the total weight of said composition.

7. (Amended) The composition of Claim 1, wherein said N-cholesteryloxy carbonyl-4-para-aminophenol is present in an amount of 0.5 to 2.5 % by weight, relative to the total weight of said composition, and said hydroquinone or [derivative thereof] hydroquinone compound is present in an amount of 0.5 to 1 % by weight, relative to the total weight of said composition.

9. (Amended) The composition of Claim 8, wherein said vesicles are dispersed in an aqueous or oily phase comprising said hydroquinone or [derivative thereof] hydroquinone compound.

10. (Amended) The composition of Claim 8, wherein said hydroquinone[,] or [derivative thereof,] hydroquinone compound is encapsulated in said vesicles.

12. (Amended) A method for depigmenting and/or lightening the skin, body hair, or head hair, comprising applying to the skin, body hair and/or head hair, a composition comprising, in a physiologically acceptable medium:

(1) N-cholesteryloxy carbonyl-4-para-aminophenol; and

(2) hydroquinone or a [derivative thereof] hydroquinone compound which has depigmenting or lightening activity.

15. (Amended) The method of Claim 12, wherein said hydroquinone or [derivative thereof] hydroquinone compound is present in said composition in an amount of 0.1 to 2 % by weight, relative to the total weight of said composition.

16. (Amended) The method of Claim 12, wherein said hydroquinone or [derivative

thereof] hydroquinone compound is present in said composition in an amount of 0.5 to 1 % by weight, relative to the total weight of said composition.

17. (Amended) The method of Claim 12, wherein said N-cholesteryloxy carbonyl-4-para-aminophenol is present in an amount of 0.01 to 5 % by weight, relative to the total weight of said composition, and said hydroquinone or [derivative thereof] hydroquinone compound is present in an amount of 0.1 to 2 % by weight, relative to the total weight of said composition.

18. (Amended) The method of Claim 12, wherein said N-cholesteryloxy carbonyl-4-para-aminophenol is present in said composition in an amount of 0.5 to 2.5 % by weight, relative to the total weight of said composition, and said hydroquinone or [derivative thereof] hydroquinone compound is present in said composition in an amount of 0.5 to 1 % by weight, relative to the total weight of said composition.

20. (Amended) The method of Claim 19, wherein said vesicles are dispersed in an aqueous or oily phase containing hydroquinone or [one of its derivative thereof] a hydroquinone compound.

21. (Amended) The method of Claim 19, wherein said hydroquinone[,] or [derivative thereof,] hydroquinone compound is encapsulated in said vesicles.--

23. (Newly Added)